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ABSTRACT

Presentations from speakers at a conference on Rett Syndrome are summarized. The presentations focused on Rett Syndrome's genetic basis and identification as a clinical syndrome, involving, among other things, mental subnormality, epilepsy, infantile spasms, hand stereotypes, and poor hand use. Also discussed were: Rett Syndrome's predictive factors; differential diagnosis; incidence; age of onset; epidemiology; studies of sleep analysis and catecholamine measurements; treatment with steroids, bromocriptine, and music therapy; ratio of male/female patients; case studies; and resulting family stress. (JDD)

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SYNOPSIS
4TH INTERNATIONAL CONFERENCE ON RETT SYNDROME
VIENNA, AUSTRIA OCTOBER 2-5, 1986

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October 3, 1986

The first speaker was John Opitz of the USA. Dr. Opitz talked about Rett Syndrome as a clinical syndrome but one which had yet not been defined as a genetic syndrome, that is with a specific molecular or biochemical defect. He discussed precedence for lesions at the Xp 21.1 locus as in Duchenne muscular dystrophy and Ornithine transcarbamylase deficiency. He also noted the location of the brain protein, synapsin, to the X chromosome on the short arm. He noted that a patient with a deletion of 18 q- had a phenotype with features similar to Rett syndrome. He concluded by saying that heterogeneity in Rett syndrome had not been substantiated but also not excluded. He went on to comment on the difference between heterogeneity and variability as is seen in the Tay-Sachs disease family, for example. He noted, in a series of patients, frequent hyper- and hypopigmentation and pigmented nevi with a halo. He posed three questions, namely: 1) does Rett syndrome involve a neural crest problem and thereby is it in the realm of a multiple congenital anomaly group, 2) is it a neuroendocrine disease, and 3) are the children really normal at birth? He suggested a standard physical examination protocol including cephalometry and anthropometry, nuclear magnetic resonance and neuroendocrine studies. He noted that in greater than a thousand cases, two are from consanguineous marriages, there are three known instances of concordant twins, there are half-sisters from Sweden and Hanefeld has two sets of whole sisters. He then reviewed the Jacobs-Smith pedigree. He also indicated that there was a normal ratio of males to females among siblings.

The next speaker was Bengt Hagberg from Sweden. He said that as of this moment there are approximately 1,100 cases, about 350 from the USA,

about 150 from Japan, about 300 from Central Europe, about 150 from the United Kingdom, about 100 Scandinavia, and about 50 to 100 from other countries. Prevalance in Southwest Sweden is 1 in 15,000 for the classical form, 1 in 45,000 for his formes frustes and an overall prevalance of 1 in 10,000. He reiterated the data with regard to the full sisters, half sisters, and the monozygotic twins indicating that there were four sets of twins. There are also three sets of dizygotic twins, one involving both females and two involving a male/female. There may also be an additional case of full sisiters from Norway which he has yet to see. He noted six instances of suspected male variants, two from America of Sakku Naidu, one which does not, one of which is suspicious; one from Finland, one from France, and two from Germany, which Hanefeld says are not Retts. In Sweden, to date, there are 62 cases of classical Rett syndrome, four forme fruste, no congenital cases, two atypical earlier severe, and 6 atypical cases, for a total of 74. Of the 62 classical cases, 53 had hand wringing and washing of the usual variety, the remaining 9 had hands apart pattern, including separate wringing, breast tapping, head tapping or scratching, mouth tapping asymmetrically, and piano playing kind of movements. He indicated that of the 4 forme fruste cases, four of four had normal pre- and peri-natal histories, one of four had decreasing head circumference, three of four had dementia, four of four had decreased hand use, two of four had stereotypic hand movements, three of four had slight apraxia-ataxia, and the diagnosis was tentative at greater than or equal to 13 years. Three of four had speech remnants and four of four had spastic extremities which developed slowly. As noted, all cases began in adolescence.

The next speaker was Hugo Moser of the Kennedy Institute in Baltimore. He described the cases which they have evaluated at the Kennedy Institute; from the United States 130 white patients and 6 black patients, 7 from Canada, 2 from Austria, 1 from Great Britian, India, and Pakistan, respectively. He noted that one tentative Rett syndrome had indeed been diagnosed as having Batten's disease. He noted that the Philadelphia twins were concordant in that HLA typing had confirmed monozygosity. He suggested that research directions should go toward cytogenetics, DNA and a rigorous protocol for neuropathological analysis. He also indicated the continued need to evaluate PET scanning in view of the fact that the D2 receptor analysis had been normal but the D1 receptor had been done in Lesch-Nyhan patients showing that this methodology is technically feasible. In addition, he pre-empted Sakku Naidu by saying that she had data from 10 patients indicating a glycolipid abnormality in plasma and urine.

The next paper was by Dr. Fukuyama who described the epidemiology in Japan. A survey of university and national hospitals for x-linked syndromes revealed a 74% response rate. There were 35 Rett syndrome patients from university facilities and 58 from national hospitals and sanitoriums for a total of 93. There were 35 Aicardi patients from university facilities and one from a national hospital or sanitorium, for a total of 36. There were no instances of consanguinity or twins. He noted that in evaluating the children, the parachute response was not present if the hands were allowed to remain together. However, if one hand was held back, the response was noted in the other hand.

The next speaker was Yoshiko Nomura. Yoshiko indicated that their studies using sleep analysis and catecholamine measurements showed a

decrease in REM sleep versus normal controls and a loss of periodicity with age. She also noted a decrease in CSF catecholamines and their metabolites. PET scanning using the glucose analogue showed decreased activity in the frontal lobe areas. Somatosensory evoked potentials showed prolonged latencies. She postulated a catecholamine serotinergic imbalance. She noted in a patient with juvenile Parkinsonism who died at age 39, there was a marked decrease in pigment in the substantia nigra with minimal gliosis, findings similar to Rett syndrome. She noted a very marked decrease in tyrosine hydroxylase, especially in the basal ganglia, the substantia nigra and the locus ceruleus. She noted that there was an age dependent change in tyrosine hydroxylase activity in the caudate but not in the substantia nigra.

The next speaker was Folker Hanefeld, West Germany, who described his experience of 20 cases that he has seen personally. The average age of onset was 5 to 32 months. He said that he had noted, in rare instances, the onset of the syndrome as infantile spasm. Steroids in these instances yield slight improvement of the Rett syndrome and the seizures were aborted. There was no special deleterious effect of the infantile spasm on the progression of the Rett syndrome. He noted the measurement of pyruvate in 6 of 20 patients, 2 of which were increased, lactate in 7 of 20 patients which was normal, and ammonia in 8 of 20, 2 of which were increased. Serum VMAs and homovanilic acid levels were normal.

The next description was by Dr. Ingered Witt-Engerstrom, Sweden. Dr. Engerstrom described the use of staging as predictive for the diagnosis of Rett syndrome indicating that the Denver Developmental assessment skills were plateauing at 9 to 10 months and definitely decreasing by 15 months. Indicators that seemed to be predictive were

plateauing of the incease of head circumference, a loss of hand skills, interest in contact, and for certain, the presence of hand stereotypies.

The next description was by Eugen Boltshauser, Switzerland. Dr. Boltshauser talked about the differential diagnosis of tachypnea-apnea and indicated a number of syndromes that are associated with tachypnea or apnea. These included Rett syndrome, Joubert syndrome, Mohr syndrome (oculofacial digital syndrome type II), Dandy-Walker syndrome, and "Private syndromes indicating multiple different etiologies". Except for Rett syndrome, the onset is at birth in all these other syndrome. Microcephaly is present in Rett syndrome only and questionably in the private syndromes, and the vermis is absent in Joubert syndrome, Mohr syndrome and the Dandy-Walker syndrome. The Joubert patients have a tendency for the breathing abnormality to improve with age. A fourth of them have occipital encephaloceles, there is an increased incidence of retinal changes, they never have microcephaly or seizures. They do have a convergent strabismus. In addition, occasionally one sees tachypnea or apnea in association with epilepsy, retardation, microcephaly, or cerebral palsy as a constellation of one or all together; also, as a normal variant and also as acquired. Joubert syndrome, in addition, has the picture of hypo- or aplastic cerebellar vermis with an increase in the fourth ventricle and an abnormal shape as well as normal size and shape of third and lateral ventricles. Neuropathology shows the same vermis aplasia as well as dysplasia and heterotopias of the cerebellar nuclei. There are also anomalies of the brain stem nuclei. Joubert syndrome is inherited as an autosomal recessive with a preponderance of cases in males for no known reason. A prenatal diagnosis may be made by ultrasound and the prognosis is not good in that about one-third die

before age 3 and the oldest patient is 25 years old. Sleep studies in these children reveals tachypnea both awake and asleep. Mohr syndrome or orofacial digital syndrome type II includes tongue hamartomas, elevated palate, hypoplastic digits with polydactyly, mental retardation is generally not present but this is variable and CT scan may show severe cerebellar atrophy.

Christopher Gilbert from Sweden was the next speaker. He described two patients less than two years of age, one with Rett syndrome and one with autism. The Rett patient was videotaped at 16 months of age showing midline hand stereotypies, autism, she appeared happy, responded to tactile stimulation but there was no change without any stimulus. The autistic patient showed stereotypies but they were not in the midline and tended to be instead in front of the eyes, one hand at a time. This child would grasp for objects unlike the Rett syndrome child. There were numerous self-stimulatory acts, including head rolling, there was less interest in the environment, an active avoidance of gaze contact and evidence of general unhappiness.

The next speaker was Dr. Toifl from Austria who described an atypical case of stereotypic motor behavior with an occipital encephalocele with ventriculomegaly treated with a shunt. This child was virtually blind and had optic atrophy. She had a spastic tetraparesis with diffuse muscular atrophy. She had stereotypic hand movements of the Rett type with hyperventilation and lumbosacral vertebral abnormalities but definitely did not have Rett syndrome.

The next speaker was John Stephenson from Scotland who indicated a prevalance of 1 in 12 to 13 thousand.

The next speaker was Francoise Goutieres, France. She indicated that in France they had seen 35 typical cases since 1972, 14 between 1972 and 1982, 12 between 1982 and 1984, and 9 between 1984 and 1986. They have also seen 14 atypical cases, 7 between 1980 and 1985, and 7 between 1985 and 1986. These children, she said, did not have Rett syndrome but had significant features making their diagnosis somewhat difficult. However, several of them had abnormal development from birth, 1 showed no regression, 1 showed slight regression, 1 showed a secondary regression at about 18 months of age. Some presented with severe seizures along with autism, hand stereotypies, poor hand use, but without hyperventilation. Microcephaly, mental retardation, and seizures were the general features and regression tended to follow the seizure onset. She described a child who had a chromosome deletion who had no autism, did have microcephaly, did have hand stereotypies, did have no or poor hand use and did hyperventilate. A child with tuberous sclerosis was autistic but had normal head circumference, did have hand stereotypies but had normal hand use and did not hyperventilate, and a child with herpetic meningoencephalitis had autism and hand stereotypies with little or no hand use and hyperventilation but did not have microcephaly.

The next speaker was John Wilson, England, who described the likely differential diagnosis at various ages. In the first year these included mental subnormality, epilepsy, infantile spasms, cerebral palsy, and congenital cerebellar ataxia. In the second year these included mental subnormality, autism, spinal cerebellar degeneration, metachromatic leukodystrophy, cerebral palsy, Angelman's syndrome and nonspecific cerebral degeneration. After the second year of life the

differential included mental subnormality, with or without epilepsy and autism, spinal cerebellar degeneration, olivopontocerebellar degeneration, progressive myoclonic epilepsy, and Friedreich ataxia. He then went on to described Angelman syndrome in some detail. It is also known as the "Happy Puppet" syndrome. These children have prominent lower jaws, midface hypoplasia, hand movements, a happy disposition, pointed pinched nose, and a non-progressive disorder. The EEG shows high amplitude slow and sharp activity with eye closure, particularly, and quieting with the eyes open. In instances where the first diagnosis is incorrect and then leads to the diagnosis subsequently of Rett syndrome, the first diagnoses include mental subnormality with or without autism, and epilepsy.

The next speaker was Michael Zapella from Italy. Dr. Zapella described treatment with bromocriptine up to 2.5 to 5 mg per day, saying that this produced increased alertness, attention and better balance, Using metaclopramide injections and blood assessments of 30 and 60 minutes thereafter, in 15 patients he found that the beta endorphins and beta lipotropin had little or no response whereas prolactin had an excessive response. He encouraged cuddling, holding, touching and placing the child in front of the parents so that stimulus was increased. His conclusion was that the bromocriptine tended to reduce the autistic traits.

The next speaker was Dr. King from United Kingdom who measured catecholamine metabolites in spinal fluid in 14 patients, ages 2 to 15. She found no differences from control. Her methodology was HPLC with electrochemical detection.

The next speaker was Vincent Riccardi from the United States who indicated that there are now 6, other than Rett syndrome, disorders transmitted by an X-linked dominant mode. He discussed the role of microdeletions and the notion of candidate genes on the X chromosome which could account for the disorder.

The next speaker was Dr. Gennaro of West Germany who indicated the existence of a gene for neuron specific protein synapsin I. Synapsin I is a neuron specific protein in both the central and peripheral nervous systems, is concentrated in the pre-synaptic terminals, and particularly is associated with synaptic vesicles. It consists of 2 proteins, one 74 and the other 78 KDa with approximately 691 amino acids. It makes up about 0.4% of brain protein. It is a substrate for cyclic AMP and for calcium/calmodulin-dependent protein kinase. The sites of the phosphorylation are known. Synapsin also interacts with cytoskeletal elements such as spectrin and actin. Its function is unknown and the question is "is it important in neurotransmitter release or for structural purposes"? Regarding its molecular genetics, the cDNA has allowed the determination of the primary protein structure and isolation of the gene for synapsin. The gene is on the X chromosome in man and mouse and at least two mRNA species exist. There are three amino acid repeats located in regions where it binds to synaptic vesicle. Rat cDNA probes recognize synapsin gene on mouse and human. The X chromosome site is at p 11.1/11.2 (Duchenne muscular dystrophy is 21.1). Expression in the nervous system indicates an age-dependent process with a 5.8 kb component present at birth, disappearing at 7 days of age, and a 4.5 kb fraction present at birth, increasing to a peak at 20 days of

age and then receding to a rather constant level at about 30 days of age. In terms of neurobiology, cells of the cerebellar granule cell layers are proliferating and migrating at the same time and as they move past the Purkinje cells to form the molecular layer they develop synapses in this molecular cell layer where the synapsin has the highest content. The plan is to analyse synapsin gene products and to do a detailed analysis of developmentally-regulated synapsin gene expression in the rat. No differences were noted in the DNA structure in Rett patients versus controls in a preliminary study.

The final speaker was Jan Wahlstrom who indicated the sex ratio is 1.11 male to female. In siblings of 192 cases there are 173 males and 156 females. Of the 62 cases in Sweden, 31 had high resolution banding and no abnormalities were noted in leukocytes. Fragile X (p22) was seen in 12.12% of Rett cells, 3.56% of autistic cells, 1.47% of others. These were in leukocytes. The recurrence risk for Rett syndrome is 0.4% which is too low to support prenatal sex determination and elective termination of pregnancy.

The second day of activity of the Rett conference was much less informative. The first speaker was Alison Kerr from Scotland who described observations during the pre-regression period. She showed a series of video tapes suggesting that the characteristic defects in Rett syndrome are already present before the initial signs of regression and that such regression begins at a given developmental age and not at a given chronological age. With regard to the cognitive profile, she felt that this was strongly related to inhibition of voluntary movement.

The next speaker with information of interest was Sakku Naidu, Baltimore. Dr. Naidu indicated that in the older patient there appeared

to be selective wasting in the lower extremities with absent to poor deep tendon reflexes in the lower extremities and with increasing rigidity. She noted that thermography performed in patients showed vasomotor instability with reduced temperature in hands and feet in a stocking and glove distribution. She further noted that a patient who had had an inadvertent unilateral sympathectomy along with scoliosis surgery, showed increased temperature and growth in the sympathectomized extremity. My editorial note on this is if this affect is related to an increase in a sympathetic tone, is it indeed increased noradrenaline activity or is it a reduction in acetylcholine activity such that there is an imbalance in the two systems?

Dr. Naidu also reported on plasma and urine glycolipid analyses in 10 children and in 5 controls from age 4 to 62 years. She noted that there was an abnormal compound accumulated which was slightly more polar or equivalent in mobility to GD_2. She stressed that this was preliminary data. The isolation procedure for extraction of the glycolipid from the plasma included extraction with chloroform methanol, 2:1 (20 volumes) followed by filtration and re-extraction of the residue with chloroform methanol, 2:1 (10 volumes), followed by filtration and re-extraction of chloroform-methanol-water, 1:2:5. The extract was dried and re-suspended in chloroform and passed over a silicic acid column. The neutral lipids were first eluted with chloroform. The glycolipids were next eluted with acetone and methanol 9:2, and finally the phospholipids were eluted with straight methanol. The first patient analyzed in the series showed an increased amount of glycolipids but one glycolipid was especially increased. It is more polar than G_{m1}, slightly more polar than or equal to G_{D2}. Although it migrated in an

area commonly shared with gangliosides, the material was negative for sialic acid. It was carbohydrate positive. Of interest in one family, the material was present in a patient and siblings but not in the parents. It was also noted in urine. Based on sphingosine analysis, there was a 15-fold increase in the glycolipid in plasma, and based on carbohydrate determination, the carbohydrate to sphingosine ratio was 7:8:1, indicating a rather long oligosaccaride chain. Fatty acid constituents were principally palmitic, stearic and oleic acid.

The next description of note was by Albertine Wesecky from Austria. Dr. Wesecky is a music therapist who indicated that music therapy had to be conducted with regularity, that the program had to be individualized to the patient and that the parents could be instructed to be involved in the treatment program.

The next speaker was Dr. Olsson from Austria. The principal information from Dr. Olson is the Randle-Short scale for autism which includes 14 items. 7 of 14 items must be met or fulfilled for the diagnosis of autism to be made. Rett children will fulfill sufficient criteria to allow the diagnosis of autism but the form of their behavior is different qualitatively. The 14 items include: 1) severe contact problems, 2) acts as if deaf but responds actively and positively to music, 3) resists invitation to learn new things, 4) no fear of real danger, 5) resistance to divergence from familiar, 6) expresses wishes through gestures, 7) giggling and laughter without evident cause, 8) rejects caressing and tenderness, 9) physical hyperactivity, 10) no eye contact, 11) excessive attachment to certain objects, 12) rotating small objects, 13) stereotypical playing habits, 14) isolation.

The next speaker was Dr. Sudge Budden, Portland. Dr. Budden stressed the role of the general physician in the care of the Rett children and indicated the need to deal with parent needs, sibling needs, and school needs. In the latter case, both correct placement and teacher education is required. Dr. Budden further noted that 5 of 14 patients had decreased hearing, 3 of 5 had conductive hearing losses, 2 of the 5 had sensorineural loss and in 1 of them it was progressive based on serial assessments.

The next speaker was Peter Riederer. Dr. Riederer is now in Wurzburg, West Germany. Dr. Riederer reiterated data previously presented indicating that tryptophan was reduced in the Rett brain in the putamen, the globus pallidus and the amygdala. It was normal in the caudate, in the raphe, and the reticular formation as well as the cingulate gyrus. Kynurenine on the other hand, was increased in all these areas. Serotonin was non-detectable in the putamen and globus pallidus and was normal in the raphe nuclei and the reticular formation. 5-Hydroxyindoleacetic acid was similarly reduced. In the substantia nigra there was an increase in DOPAC and a decrease in dopamine and homovanilic acid. The homovanilic acid to dopamine and the DOPAC to dopamine ratios were both increased. Similar data were described for the claudate nucleus and for the putamen. Spiroperidol binding in the putamen showed a B_{max} to be 27% of the control value and the K_D to be 78% of the control. Ferritin was decreased 57% in the putamen and frontal cortex but not in the globus pallidus where it was 97% of control values. Dr. Riederer queried whether the decrease in ferritin was related to a decrease in iron binding proteins or a decrease in cholinergic neurons which seem to include the iron binding

proteins. Spiroperidol binding in Parkinson's disease and progressive senile dementia of Alzheimer type was within normal limits. Ferritin binding was also within normal limits. Dr. Riederer measured ascorbic acid and found it to be 49% of control values for putamen, less than 1% in the claudate, 22% in the globus pallidus, and 14.8% in the raphe nuclei. Glutathione, another reducing agent, was 50% of controls in the putamen, 63% in the claudate, 26% in the globus pallidus, 40% in the raphe, 7.5% in the cerebral parietal cortex, and 67% in the occipital cortex. In the redox system ascorbate and glutathione are inter-related closely.

The next speaker is Dr. Killian, Austria, who noted that the iron related parameters are important for tyrosine hydroxylase activity particularly iron in the reduced state. He further noted that the X chromosome codes for at least 2 of the 12 polypeptide sites were ferritin. He noted that iron deficiency is associated with reduction in ferritin levels. Serum assay for ferritin in 19 patients revealed reductions in 4 that were iron deficient. Among the others, there was no difference from controls for the ferritin levels. Hence, low serum ferritin levels are not markers for Rett syndrome. This specific data indicated that in all groups of children studied, iron was reduced only in association with anemia, transferrin was normal and that ferritin levels were 27.6 between the ages 1 to 6 for patients, 19.4 in the controls for that age with the ranges being 1 to 65 and 10 to 39 respectively. For the 6 to 14 age group, the control mean was 26.3 with a range of 12 to 73 and the patient mean was 24 with a range of 14 to 40. In the 14 to 27 year old group, the control mean was 32.4 with a range of 15 to 112, and the patient mean was 28.6 with a range of 0 to 86.

Susan Goodship from Scotland then described stress in the family indicating that pressures differ in different persons and at different ages. Despite the severe involuntary movements, she wondered whether there were voluntary movements within this involuntary act that could be exposed in therapy. One note of comment in discussion, Hugo Moser noted that there were already active parent groups in Huntington disease, Alzheimer disease and learning disability (Orton Society). Bengt Hagberg noted that biopterin measured in urine, blood and CSF was normal but there was a question of abnormality in dihydropteridine reductase. A consensus was reached that it was necessary to obtain post mortem tissue, not only of brain, muscle and nerve, but also of liver, kidney and others, and to keep it in the fresh frozen state for subsequent biochemical analyses. The glycolipid finding noted above was discussed in relationship to glycosphingolipids as cell recognition markers and perhaps the deviations from normal might represent abnormal cell-cell contacts.